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Original article

Emerging souvenirs—clinical presentation of the returning traveller with imported arbovirus infections in Europe

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ABSTRACT

Background: Arboviruses are an emerging group of viruses that are causing increasing health concerns globally, including in Europe. Clinical presentation usually consists of a nonspecific febrile illness that may be accompanied by rash, arthralgia and arthritis, with or without neurological or haemorrhagic syndromes. The range of differential diagnoses of other infectious and noninfectious aetiologies is broad, presenting a challenge for physicians. While knowledge of the geographical distribution of pathogens and the current epidemiological situation, incubation periods, exposure risk factors and vaccination history can help guide the diagnostic approach, the nonspecific and variable clinical presentation can delay final diagnosis.

Aims and sources: This narrative review aims to summarize the main clinical and laboratory-based findings of the three most common imported arboviruses in Europe. Evidence is extracted from published literature and clinical expertise of European arbovirus experts.

Content: We present three cases that highlight similarities and differences between some of the most common travel-related arboviruses imported to Europe. These include a patient with chikungunya virus infection presenting in Greece, a case of dengue fever in Turkey and a travel-related case of Zika virus infection in Romania.

Implications: Early diagnosis of travel-imported cases is important to reduce the risk of localized outbreaks of tropical arboviruses such as dengue and chikungunya and the risk of local transmission from body fluids or vertical transmission. Given the global relevance of arboviruses and the continuous risk of (re)emerging arbovirus events, clinicians should be aware of the clinical syndromes of arbovirus fevers and the potential pitfalls in diagnosis. **I. Eckerle, Clin Microbiol Infect 2018;•:1**

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Introduction

With an increase in global travel rising to around 950 million persons per year, physicians are frequently confronted with patients potentially infected with exotic pathogens [1]. Besides malaria, infection with an arbovirus is a common cause of fever in

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travellers returning to Europe [2]. Arboviruses are a large group of emerging RNA viruses spanning different virus families and genera that are responsible for human disease worldwide in the range of hundreds of million cases annually [3–5].

In Europe, several endemic arboviruses are of clinical importance such as tick-borne encephalitis, West Nile fever, Crimean-Congo haemorrhagic fever and sand fly fever [6]. However, there is heterogeneity in the surveillance of endemic, well-known arboviruses and uncertainty about the true burden of related illness in Europe [6]. The situation is aggravated by (re)introduction of vectors as well as introduction of viraemic patients after travel [5–8]. Limited autochthonous outbreaks have been described for dengue virus (DENV) [9–13] and chikungunya virus (CHIKV) in Europe [14–16]. The endemic areas for DENV and CHIKV are found in tropical and subtropical regions of the world. DENV is the most successful arbovirus in terms of emergence in recent decades, with an estimated 390 million infections per year globally [17]. The main endemic areas are in Asia and South America, with less data in some areas, particularly in Africa. Returning travellers presenting with DENV can serve as sentinels, and a recent study estimated the proportion of cases in Africa to be in the same range as in Latin America [17–19]. CHIKV is mainly found in Asia and Africa, with recent large outbreaks on the Indian Ocean islands, and has spread to the New World, particularly the Caribbean and the Americas [20–22].

Zika virus (ZIKV) was considered to be a flavivirus of low interest until its dramatic emergence in French Polynesia in 2013 and subsequently in South America in 2015. While Zika usually causes mild disease in adults, it can lead to congenital malformations when infecting pregnant women and is also associated with Guillain-Barré syndrome [23]. This has led to increased awareness of the potential risk of other neglected arboviruses [5]. Fortunately, no vector-borne transmission of ZIKV has been recorded in Europe to date [6]. However, sexual transmission of ZIKV has been reported and is an additional source of introduction besides vectors and travellers with disease [24,25].

While dengue, Zika and chikungunya account for the vast majority of travel-imported arbovirus cases in Europe, there is a plethora of other, less well-known arboviruses capable of causing human disease. These include viruses such as Jamestown Canyon, Mayaro, Oropouche, Tahyna and Usutu viruses—and many more which are not known to most clinicians [26–28]. The increasing importance of arboviruses in Australia, such as Kunjin virus, Murray



Fig. 1. Blanching rash of dengue fever in returning traveller.

Valley fever and Ross River fever, poses an underrecognized hazard for travellers from Europe [29,30].

For clinicians, the diagnosis of travellers presenting with syndromes of fever, rash (Fig. 1), myalgia, arthralgia and headache is challenging because of their nonspecific nature and the wide range of potential differential diagnoses. Diagnostic test strategies for arboviruses can be complex as a result of the short viraemic period, pitfalls in serology such as high levels of antibody cross-reactivity and patchy access to specialized arbovirus diagnostics. Despite similarities in the disease presentations, there are differences which, together with travel and vaccination history, can help guide identification, sampling and differential diagnosis.

We present three cases to highlight the difficulties which European clinicians face in recognizing travel-related imported arbovirus illnesses, and we discuss similarities and differences in clinical and laboratory findings.

Imported arbovirus infections to Europe

Case 1: Imported chikungunya case in Greece

In spring 2016, a woman in her 20s returned to Greece from Recife, Brazil, where she had stayed since November 2015. During her return travel, she developed myalgia and arthralgia for 9 days, followed by development of high fever (temperature 40°C) and mild headache upon arriving in Greece. There was no significant medical or surgical history. At physical examination, there was no rash, hepatosplenomegaly or conjunctivitis, but she had swelling of both knees and the left wrist. Her white blood cell count was $3.2 \times 10^9/L$ with 50% neutrophils, 34% lymphocytes and 13% monocytes, haematocrit 39.5%, platelet count $247 \times 10^9/L$ and C-reactive protein 10 mg/dL (normal <5 mg/dL). All other tests were unremarkable. Her fever subsided over the following 72 hours, with normalization of her laboratory tests, and she was discharged after 3 days of hospitalization. She was advised to adopt safe-sex practices until results for ZIKV were received.

Molecular testing for DENV, ZIKV and CHIKV was performed at the National Reference Centre for Arboviruses in Greece on the samples taken on the second day of illness using commercial Real Time RT-PCR kits (Altona Diagnostics, Hamburg, Germany). CHIKV RNA was detected in serum and blood. An in-house nested reverse-transcriptase PCR using generic alphavirus primers [31] obtained sequence clustering in the ESCA genotype. The sequence showed 100% identity to sequences from Brazil [32]. The presence of CHIKV IgM and IgG antibodies was tested using indirect immunofluorescence test and enzyme-linked immunosorbent assay (ELISA), respectively (Euroimmun, Lübeck, Germany). A weakly positive result was obtained only for CHIKV IgM antibodies in the initial sera, while both IgM and IgG antibodies were detected in a convalescent sample taken on Day 10 of illness. Serology for DENV and ZIKV remained negative. CHIKV was isolated from her blood in Vero E6 cells, with cytopathic effects seen on the second day after inoculation. The patient had an unremarkable recovery, although arthralgia persisted for 3 more months.

Case 2: imported dengue fever case in Turkey

A 24-year-old French national presented in November 2017 at the Koç University Hospital, Istanbul, with a 3-day history of fever, fatigue and malaise, starting 4 days after returning from a 9-month residence in Cambodia.

At admission, his temperature was 38.9°C, his blood pressure was 130/70 mm Hg and he had a right subconjunctival haemorrhage. No rash or hepatosplenomegaly was detected, and other physical examination findings were normal. Laboratory tests

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